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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/095,639	06/11/98	POZZILLI P	515-4111

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EXAMINER	
SCHNIZER, R	
ART UNIT	**PAPER NUMBER**
1632	7

DATE MAILED: 11/22/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

FILE COPY

Office Action Summary

Application No.	Applicant(s)
09/095,639	~~Pozzilli~~ Pozzilli
Examiner	**Group Art Unit**
Richard Schnizer	1632

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-11 and 16-20* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-11 and 16-20* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 6

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

Lack of Unity

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in response to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-11 and 16, 19, and 20, drawn to milk products comprising non-immunogenic β-casein and a first method of making them.

Group II, claim(s) 17 and 18, drawn to a second method of making milk products lacking non-human β-casein .

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The technical feature which links the groups is a milk product comprising non-immunogenic β-casein, wherein said immunogenicity is directly related to defined amino acid sequences not found in human β-caseins. However, this technical feature is anticipated by human milk and a variety of patented compositions such as the human infant formula of WO 91/06875. Therefore the technical feature linking groups I and II does not define a contribution over the prior art and cannot be considered a special technical feature as defined by PCT Rule 13.2.

The special technical feature of group I is considered to be milk products comprising β-caseins which lack the immunogenic sequences described in the specification, and methods of making the products in which non-human β-caseins are eliminated at the genetic level. The appropriate β-caseins are then synthesized separately and added, or are added by genetic means such as the construction of a transgenic animal which comprises the appropriate β-casein gene.

The special technical feature of group II is considered to be methods of making milk products comprising β-caseins which lack the immunogenic sequences described in the specification, wherein immunogenic β-caseins are removed from the composition by chemical-physical means.

Accordingly, groups I and II are not linked by the same or a corresponding special technical feature and do not form a single general inventive concept.

Although a lack of unity has been found, the claims have been searched in their entirety, and all claims are under consideration in this Office Action. No further fee for consideration of group II is required.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Italy on 12/27/95. It is noted, however, that applicant has not filed a certified copy of the application as required by 35 U.S.C. 119(b).

Claim Objections

Claim 5 is objected to because of the following informalities: The claim is not written in proper Markush form. Specifically, the last group is not separated from the penultimate one by the conjunction "and". Appropriate correction is required.

Claims 6, 7 and 16-20 are objected to because of the following informalities: The claims are ungrammatical. Claim 6 recites the word "pharmaceuticals" instead of "pharmaceutical", and each of claims 7 and 16-20 should begin with an article, such as the word "a".

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 2, and 4-10 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The invention is milk, or a composition derived from milk, which has less than 10% b.w. non-human β-caseins (claims 1, 2, 4-8, and 10). Alternatively, the invention is milk, or a composition derived from milk, wherein the composition lacks β-casein and is produced by an animal which is genetically modified (claim 9).

Claims 1, 2, 4-8, and 10 are drawn to non-statutory subject matter because they encompass naturally occurring human milk. It is noted that claim 10 is a product-by-process

claim in which the process receives little patentable weight, resulting in a claim encompassing naturally occurring human milk. The specific sequence limitations imposed by claims 4-8 of the instant application are met by natural human β-casein, the sequence of which is disclosed in WO 93/04171.

Claim 9 is drawn to non-statutory subject matter because milk naturally lacking beta casein is produced by goats which are homozygous for a naturally occurring genetic modification consisting of a null mutation at the β-casein locus. See abstract of Chianese et al (Lait 73(5-6): 533-547, 1993.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 and 16-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Enablement is considered in view of the *Wands* factors (MPEP 2164.01(a)).

Nature of the invention. The invention comprises products, and methods for producing the claimed products, wherein the utility of the invention is the use of the claimed products in diets for the prevention of insulin-dependent diabetes (IDDM). The essence of the invention is

the hypothesis that non-human β-caseins can cause immune responses in humans. Specifically, the presence in infant formula of a hexapeptide sequence common to both bovine β-casein and human GLUT 2 can cause an autoimmune response wherein anti-bovine β-casein antibodies recognize GLUT 2 on insulin-producing cells. This immune response is thought to lead to IDDM.

State of the prior art. The state of the prior art is set forth in Cavallo et al (Lancet 348(9032): 926-928, cited in the application. Cavallo teaches that 51.1 % of IDDM patients exposed to bovine β-casein responded with a proliferation of T-lymphocytes, whereas only 2.7% of healthy controls showed the same response (page 926, column 1, paragraph 3). Sequence homology exists between bovine β-casein and several molecules expressed by insulin-producing β cells, including p69, carboxypeptidase, and GLUT 2. In further support of an autoimmune hypothesis of IDDM, immunological cross-reactivity exists between bovine serum albumin and p69 in IDDM patients, and GLUT 2 autoantibodies have been described in patients with recent-onset IDDM (page 927, last paragraph).

Breadth of the claims. The claims are drawn to prevention of IDDM in all patients, regardless of their immune response to non-human β-casein.

Guidance and exemplification in the specification. Cavallo teaches that approximately half of the patients with IDDM have no apparent immune response to bovine β-casein. It seems that these patients are unlikely to suffer from an autoimmune problem wherein anti-β-casein antibodies recognize GLUT 2 or any other β-cell antigen.. The specification does not teach or

provide examples as to how to prevent IDDM in these individuals using the compositions of the instant invention.

Predictability of the art. Neither the prior art nor the specification eliminates the possibility that IDDM is caused by an immune-response to peptides which mimic carboxypeptidase or p69, rather than GLUT 2. In fact, Cavallo suggests that bovine serum albumin may give rise to antibodies that recognize p69, providing support for a competing autoimmune hypothesis. Further, the idea that IDDM is caused by such an autoimmune response is regarded by those skilled in the art as only a hypothesis, rather than an established fact. Thus, the predictability in the art is extremely low.

Amount of experimentation required. In order to establish that IDDM can be caused by bovine β-casein-induced autoimmunity to GLUT 2, to determine which cases are caused this way, and then to prevent IDDM in patients who show no immune response to bovine β-casein, a skilled artisan would have to perform extensive experimentation.

Because the hypothesis of an autoimmune mechanism of IDDM is unproven; because the prior art teaches that proteins other than GLUT 2 could be the target of such an autoimmune mechanism; and because the specification does not teach how to prevent IDDM in individuals who show no immune response to bovine β-casein, a skilled artisan would have to perform undue experimentation in order to successfully prevent IDDM in all individuals by using the claimed compositions.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5, 6, 8,16, 19, and-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2, 6, and 8 are indefinite because the phrase "non-human mammals resulting immunogenic in view of..." is ungrammatical, and because "the GLUT 2 protein" is recited without antecedent basis.

Claims 5, 11, and 16 are indefinite because they recite "the homologous sequence" without antecedent basis. These claims are also indefinite in their recitation of "related mixtures". It is not clear what is intended by this term because it is not defined in the specification. Thus, a skilled artisan is not apprised of what constitutes a "mixture", nor of the criteria for determining if a mixture is "related".

Claim 8 is indefinite because it recites the phrase "genetically not producing proteins". It is suggested that this phrase be replaced with the phrase "unable to produce caseins".

Regarding claim 11, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claims 11, 16, 19 and 20 are drawn to methods for obtaining a dietary product, but each fails to recite appropriate process steps detailing how that product should be obtained. For example: claims 11, 19, and 20 recites no process steps at all for obtaining the desired composition; and claim 16 recites a method of obtaining a protein by "cloning methods", but recites no steps involving gene expression or protein isolation. Cloning methods can only result in the isolation of clones or the production of organisms.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international applicationby another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-6, 8, 10, 11, 16, 19, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Bergstrom et al (WO 93/04171, published 3/4/93), cited in the application.

Bergstrom teaches milk from a non-human transgenic mammal comprising a recombinant human β-casein. The transgenic mammal's natural β-casein gene has been replaced by an

expression construct that encodes the human β-casein gene. Bergstrom also teaches the production of recombinant human β-casein in yeast and bacteria, its purification from these sources, and its use as a nutritional supplement. The amino acid sequence of β-casein, as disclosed by Bergstrom, comprises SEQ ID No.5 of the instant invention, and lacks SEQ ID Nos. 1-4, 7 and 8. See page 15, last paragraph, through page 17, first paragraph; page 22, lines 1-21; paragraph bridging pages 23 and 24; page 24, lines 16-23; page 25, lines 9-22; see also claims 27, 33 and 38-42 on pages 51 and 52.

Thus, Bergstrom anticipates the claims.

Claim 9 is rejected under 35 U.S.C. 102(b) as being anticipated by Chianese et al (Lait 73(5-6): 533-547, 1993).

Chianese teaches milk derived from goats which comprise a genetic modification causing them not to express β-casein.

Thus, Chianese anticipates the claim.

Claims 1-8, 10, 16, and 20 are rejected under 35 U.S.C. 102(e) as being anticipated by Mukerji et al (US Patent 5,643,880, filed 5/26/94).

Mukerji teaches a pharmaceutical composition comprising proteolytic fragments of human β-casein and lacking non-human β-caseins. The human β-casein DNA sequence disclosed in

Mukerji encodes SEQ ID No.5 of the instant invention, and does not encode SEQ ID Nos. 1-4, 7 and 8. See abstract; column 6, lines 10-20; and SEQ ID No. 1.

Thus, Mukerji anticipates the claim.

Claims 17 and 18 are rejected under 35 U.S.C. 102(a) as being anticipated by Le Magnen et al (US Patent 5397577, issued 3/14/95).

Le Magnen discloses methods of removing β-casein from milk and from milk by-products by membrane filtration (paragraph bridging columns 1 and 2), chromatography (separation of β-casein from milk by-products, column 6, lines 1-15, and Fig. 6), and differential solubility, column 2, lines 32-42). The non-β-casein-containing coproduct of the differential solubility technique is explicitly disclosed as having functional, physiological, and nutritional properties (column 3, lines 54-60), and the non-casein-containing chromatography fractions comprise minerals such as calcium which are similarly beneficial.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday-Friday from 7:30 to 4:00 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached at 703-308-2035. The FAX phone number for art unit 1632 is 703-308-0294.

Inquiries of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Richard Schnizer, Ph. D.

Jasemine C. Chambers

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